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TITLE: Evaluation of Feasibility for a Case-Control Study of Adrenal Androgen Production in Postmenopausal Women with Breast Cancer

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13. ABSTRACT (Maximum 200 Words) <p><u>Background:</u> Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer. Dehydroepiandrosterone sulfate (DHEAS) is secreted by the adrenals, and elevated serum DHEAS levels in postmenopausal woman who develop breast cancer suggest increased adrenal androgen production. <u>Objective/Hypothesis:</u> Evaluate feasibility of conducting a case-control study that uses adrenocorticotropin (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens in response to ACTH compared to unaffected women. Hypotheses to be tested in the full-scale study are: 1) greater adrenal responsiveness to ACTH contributes to elevated serum androgens and estrogens in postmenopausal women who develop breast cancer; and 2) increased adrenal androgen production in postmenopausal women with breast cancer is related to increased enzyme activity at a specific step in steroidogenesis. <u>Specific Aims:</u> Specific aims of the feasibility study are: 1) determine feasibility of a full-scale study; 2) gather preliminary data on basal and ACTH stimulated serum androgen and estrogen concentrations in women with breast cancer compared to controls. <u>Key Research Accomplishments:</u> 1) phase 1, which included seven healthy controls, was completed; 2) currently recruiting for phase 2, which includes healthy spouses of men with cancer.</p>			
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Introduction: Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer. Dehydroepiandrosterone sulfate (DHEAS) is secreted only by the adrenals, and elevated serum DHEAS levels in postmenopausal women who develop breast cancer suggest increased adrenal androgen production. The objective of the pilot study is to evaluate the feasibility of conducting a case-control study that uses adrenocorticotropic hormone (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens, which are converted to estrogens in peripheral tissues, in response to ACTH stimulation compared to unaffected women. Hypotheses to be tested in the full-scale study are: 1) greater adrenal responsiveness to ACTH contributes to elevated serum concentrations of androgens and estrogens in postmenopausal women who develop breast cancer; and 2) increased adrenal androgen production in postmenopausal women with breast cancer is related to increased enzyme activity at a specific step in steroidogenesis rather than to generalized enhancement of adrenal androgen production. Cellular immune function also has been hypothesized to play a role in breast cancer etiology, and cortisol, which is another hormone that is secreted by the adrenals, is immunosuppressive (i.e., causes significant decreases in numbers and percentages of lymphocytes in the blood). At no additional cost to DOD we are also collecting preliminary data to begin to address the hypothesis that greater adrenal responsiveness to ACTH contributes to greater immunosuppression in postmenopausal women who develop breast cancer.

Body: Research accomplishments are described for each task outlined in the approved statement of work.

Task 1. Prepare for data collection, Month 1-2

- a. *Finalize data collection protocol and forms.* This activity has been completed and all questionnaires have been approved by both the FCCC IRB and the DOD IRB.
- b. *Finalize database design and data entry screen.* This activity has been completed.
- c. *Hire and train study coordinator.* This activity has been completed.

Task 2. Identify and recruit participants, Months 2-6

- a. *Search FCCC Breast Evaluation Clinic and breast surgical consultation visit summaries each day to identify potential cases and benign breast disease controls.* The FCCC IRB required that we conduct the study in phases – recruiting and conducting dexamethasone suppression and ACTH stimulation studies on healthy controls during the first phase, on spouses of cancer patients during the second phase, and on women who had breast cancer during the third phase. Phase I has been completed. A FCCC Data Safety and Monitoring Board and the DOD IRB reviewed results after Phase I and will continue to review results for each phase before we can proceed to the next phase. Note that benign breast disease controls have been replaced by spouses of cancer patients to control for chronic psychological stress associated with being diagnosed with cancer or with a spouse being diagnosed with cancer. There also was concern that benign breast disease controls may not be appropriate because elevated hormone levels have been associated with benign breast

- disease in some studies. This was approved in the original protocol submitted to the DOD.
- b. *Obtain physician approval to contact cases and benign breast disease controls.* For the reasons described above under (a), this activity has not been initiated.
 - c. *Identify one friend control who is eligible and agrees to participate for each case:* Friend controls have been replaced with healthy community controls because of the IRBs concerns about asking cases to identify friends who did not have breast cancer. This was approved in the original protocol submitted to the DOD.
 - d. *Perform approximately 60 telephone interviews.* This was completed for Phase I of the study. Seven women interested in Phase 2 called FCCC for information regarding the study. Of these women, 2 were not eligible, 2 were not interested after receiving more information, 2 were not eligible at the present time, and 1 woman was eligible, but unresponsive to follow up calls.
 - e. *Send approximately 30 follow-up letters.* Completed for Phase 1. Five follow up letters were sent for Phase 2 to the women eligible and interested in the study.

Task 3. Conduct data collection visits, Months 2-8.

- a. *Administer 27 questionnaires.* Seven questionnaires have been administered.
- b. *Measure heights and weights of 27 participants.* Heights and weights of 7 participants have been measured.
- c. *Perform 27 ACTH stimulation tests, collect and store serum specimens.* ACTH stimulation tests have been performed on 7 participants. The specimens are currently being stored at the FCCC biosample repository.
- d. *Extract DNA from lymphocytes for 7 participants and store.* DNA has been extracted from lymphocytes for 7 participants and is being stored at the FCCC biosample repository.
- e. *Key and verify data.* Data has been keyed and verified for 7 participants.

Task 4. Create serum and plasma pools for laboratory quality control, Month 8. This task will be done when we get closer to conducting laboratory analyses.

Task 5. Measure the ACTH concentration in plasma and DHEAS, DHEA, androstenedione, testosterone, estradiol, concentrations in serum from 27 participants, Months 9-10. This task will be done after conduct of dexamethasone suppression and ACTH stimulation studies. Note that the FCCC IRB required that we perform interim analyses of DHEA after each phase of the study before progressing to the next phase and obtain approval of the Data and Safety Monitoring Board before progressing to the next phase. The DOD IRB has required that they also review the results and approve before we proceed.

Task 6. Analyze data and write reports, Months 11-12. This task will be completed in the future.

- a. Perform statistical analyses
- b. Write final report
- c. Begin writing grant proposal for full scale study

Key Research Accomplishments: The FCCC IRB required that the study be conducted in 3 phases and this modification was approved by the DOD IRB. The first phase includes 7 healthy control women, the second phase includes 7 healthy spouses of men with cancer, and the third phase includes 10 women who have had breast cancer.

- Phase 1 has been completed.
- Recruitment has begun for phase 2 of this study.
 - Two women have been identified as being eligible in the upcoming months for Phase 2.

Reportable Outcomes: None at this time.

Conclusions: This is an interim report for a pilot study. Based on our experience to date, it appears that we will be able to recruit healthy controls for a full scale case-control study. It remains unclear whether we will be able to recruit healthy spouses of men with cancer and women who have had breast cancer for a full scale study. If feasible, this would be one of the first studies to examine, in an integrated approach, the interrelationships of hormonal and immune responses to adrenal suppression and stimulation in women with breast cancer in comparison to healthy controls. Identification of a role for the adrenals in the etiology of breast cancer in postmenopausal women could ultimately lead to detection of populations at an increased risk of breast cancer, provide an approach to screening for women at increased risk, and/or lead to chemopreventive strategies that target the responsible enzyme or regulatory protein.

References: None at this time.

Appendices: None at this time.